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Review article

Attributes of alternatively activated (M2) macrophages

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ABSTRACT

Macrophages are cells of innate immunity and are derived from circulating monocytes and embryonic yolk sac. They exhibit high plasticity and polarize functionally in response to stimulus triggering it into classically activated M1 macrophages and alternatively activated M2 macrophages. This review summarizes markers of M2 macrophages like transmembrane surface receptors and signaling cascades initiated on their activation; cytokine and chemokine repertoires along with their receptors; and genetic markers and their involvement in immunomodulation. The detailed discussion emphasizes the role of these markers in imparting functional benefits to this subset of macrophages which define their venture in various physiological and pathological conditions.

1. Introduction

1.1. Mononuclear phagocytes

The mononuclear phagocytic system comprises of circulating monocytes in the blood and macrophages in the tissues. Hematopoiesis, i.e., the process of formation of blood takes place in the bone marrow of the long bones. In this process, granulocytes-monocyte progenitor cells differentiate into mature monocytes and circulate for approximately 8 h. During this circulation, they grow in size and finally localize into specific tissues [1]. The differentiation of monocytes to macrophages involves cell enlargement, increase in number and complexity of intracellular organelles, increase in phagocytic potential and increase in levels of hydrolytic enzymes and other soluble factors [2].

1.2. Macrophages

Macrophages are found throughout the body. Some reside in tissues, becoming fixed macrophages and others are motile called free or wandering macrophages. The mode of movement taken up by these cells is amoeboid movement. They have different names in different tissues [3].

(i) Intestinal macrophages in the gut
(ii) Alveolar macrophages in the lung
(iii) Histocytes in connective tissues
(iv) Kuffer cells in the liver
(v) Mesangial cells in the kidney
(vi) Microglial cells in the brain
(vii) Osteoclasts in bone

1.3. Origin of macrophages

Macrophages were initially disputed in the context of their origin. Furth and Cohn investigated the relationship between free and fixed mononuclear phagocytes and showed that macrophages in tissues are derived from monocytes [4]. Hence they defined circulating monocytes as the originator of macrophages. But, later new finding came in light, citing the presence of macrophages in yolk sac even before the beginning of hematopoiesis. This disproved the circulating monocytes as an absolute source of macrophages. Eventually, embryonic phagocytes were classified as the second source of tissue fixed macrophages because microglial cells in the brain and Langerhans cells originate from yolk sac [5]. Table 1 summarizes the origin of macrophages residing in major organs.

1.4. Functions of macrophages

Macrophages aid in innate immunity. They play an important role in tissue development, inflammation anti-pathogenic defense, homeostasis, cancer, and organ transplant. The major functions of macrophages are listed below.

(i) **Phagocytosis**: Macrophages engulf and digest viruses, bacteria, and foreign particles. Receptors on macrophage surface bind with Fc region of ligand molecule on the target pathogen or dead cells. As

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Table 1
Origin of macrophages of specific tissues.

Organ	Macrophage	Source
Brain	Microglial cells	Yolk sac
Liver	Kuffer cells	Yolk sac Embryonic hematopoietic stem cells
Lung	Alveolar macrophages	Embryonic hematopoietic stem cells
Intestine	Interstitial macrophages	Adult hematopoietic stem cells
Skin	Langerhans cells Dermal macrophages	Yolk sac Embryonic hematopoietic stem cells Adult hematopoietic stem cells
Heart	Cardiac macrophages	Yolk sac Embryonic and adult hematopoietic stem cells
Kidney	Mesangial cells	Embryonic and adult hematopoietic stem cells
Peritoneum	Peritoneal macrophages	Embryonic hematopoietic stem cells
Blood	Monocytes	Adult hematopoietic stem cells

The adult hematopoietic stem cells are replaced by circulating monocytes.

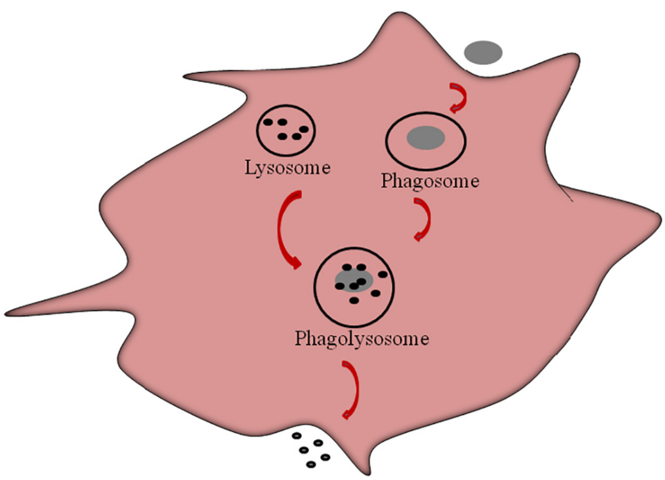

Fig. 1. Mechanism of phagocytosis.

the binding gets progressive, the membrane of macrophage engulfs the target. This results in the formation of phagosome which fuses with lysosome leading to digestion of target. Fig. 1 demonstrates the process of Phagocytosis [6].

(ii) **Antigen Presenting cells (APCs)**: Degraded foreign material or fragments of antigens are displayed on the macrophage cell surface in association with class II MHC molecules. This activates the T-cells thereby altering the adaptive immunity [7].

(iii) **Cytokine production**: Macrophages are a source of a number of cytokines involved in immune response, homeostasis, and inflammation. Macrophages secrete a large number of cytokines, which includes IL-1, IL-1RA, IL-8, IL-10, IL-12, TNF-α, INF-α, INF-γ, MCP-1, MCP-3, MIF, M-CSF, G-CSF. These modulate most of the functions of macrophages and surface marker expression [8].

1.5. Polarization of macrophages

Macrophages undergo functional polarization to respond to the stimulus triggering their activation. Macrophage polarization is associated with changes in effector molecules, receptor expression and cytokine profile [9].

Classification of macrophages:

(i) **Classically activated M1 macrophages**: Stimulation by INF-γ give rise to macrophages with M1 phenotype. Characteristic features of M1 macrophages:
(a) Increased levels of pro-inflammatory cytokines like IL-1, IL-6, and TNF-α
(b) High production of nitrogen and oxygen intermediates, i.e. peroxynitrite ($ONOO^-$) and superoxide anion (O^{2-})
(c) Anti-microbial and anti-tumor activity

(ii) **Alternatively activated M2 Macrophages**: Macrophages when stimulated by IL-4, IL-10, IL-13, and glucocorticoids polarize to M2 phenotype. Characteristic features of M2 macrophages are:
(a) Prevention of expansion of parasite
(b) Remodeling of tissue architecture
(c) Progression of tumor
(d) Exhibit immunoregulatory effect.

This development of two different subsets of macrophages is important for these cells to carry out their designated functions and thus functional polarization is the hallmark of mononuclear phagocyte system [10].

2. M2 macrophages

M2 macrophages are characterized by efficient phagocytic activity [11] because of the increased expression of scavenging receptors like mannose and galactose receptors [12] and produce ornithine by the arginase pathway [13]. M2 macrophages are said to have IL-10^{high}, IL-12^{low}, IL-1 decoy receptor^{high} phenotype [14]. M2 macrophages are further classified into three categories M2a, M2b, and M2c phenotypes.

(i) Macrophages stimulated by IL-4 and IL-13 embrace M2a phenotype and are termed as alternatively activated macrophages,
(ii) Macrophages stimulated by immune complexes and bacterial lipopolysaccharides adopt an M2b phenotype known as type II macrophages.
(iii) Macrophages triggered by TGF-β and glucocorticoids assume M2c phenotype called as deactivated macrophages [15].

Recent studies on co-culture of murine breast cancer cells, 4T1 cells and murine macrophages Raw cells demonstrated that IL-6 in the supernatant induces the generation of M2d macrophages characterized by CD80, CD86, MHC-II, and IL-15. Although in tissues a mixed population of these cells may co-exist [16]. All these M2 macrophages can minimize immune response and enhance tissue repair [17].

We will further discuss the attributes of M2 macrophages as a whole. The review will focus on how these specific markers are associated with the functionality of M2 macrophages in physiological and pathological conditions. The review focus on the attributes listed in Table 2.

2.1. Functional markers

Functional markers are actually genetic markers identified by gene mapping using techniques like PCR and microsatellite analysis and hence can also be called a DNA marker. A small region of DNA that shows sequence polymorphism can be a DNA marker. It should be sensitive, i.e., it should be linked to a specific function in question and should be single locus preferably [18].

2.1.1. Arginase-1

It is also known as arginine amidase, canavanae, and arginine transamidase. It is a manganese-containing enzyme involved in urea cycle where it hydrolyzes L-arginine to L-ornithine and urea. It exists in two isoforms arginase-I and arginase-II having similar functions but different cellular localization [19]. Expression of arginase in myeloid cells was discovered in the late '80s in mice tumor models [20]. Nathan

Table 2
Markers of M2 macrophages.

Type of marker	Names of markers	Physiological roles	Pathological roles
Functional markers	1. Arginase-1	Cellular proliferation and repair by providing ornithine.	1.Promotes growth of pathogens by providing polyamines 2. Enhances oxidative stress in CVS disorders. 3. Promotes tumor growth and angiogenesis.
	2. COX-2	1. Renin production 2. Determines brain structure 3. Maintains gastric integrity	1. Inflammation and PGE2 Production 2. Promotes tumor cell survival and metastasis.
	3. SOCS	1. Inhibition of cytokine signaling. 2. Inhibit T-cell differentiation 3. Critical regulator of post natal growth 4. Fetal liver hematopoiesis.	Members of SOCS family are associated with allergy, autoimmune diseases, inflammation, and cancer.
Surface markers	1. CD206 (mannose receptor)	It is important for phagocytosis as it recognizes carbohydrates on yeast, Mycobacterium, and other bacteria.	1. *L. donovani* uses MR for internalization in macrophages. 2. *M. tuberculosis* blocks MR to inhibit its phagocytosis. 3. MR positive macrophages assist metastasis and angiogenesis in cancer.
	2. CD163	1. Removes free hemoglobin which is toxic. 2. Role in erythropoiesis. 3. Recognition of bacteria 4. Immune regulation by inhibiting T-cell activation	1. sCD163 is a marker for leishmaniasis and Crohn's disease. 2. CD163 expressing tumor-associated macrophages have low apoptotic activity and promotes local recurrence.
	3.Scavenger receptor A	1. Recognizes LDL and clears it. 2. Clear apoptotic bodies and immature thymocytes. 3. Aids in adhesion of macrophages	1.Contributes to atherogenesis 2. Induces septic shock
	4. CD204 (scavenger receptor B)	Acts as a cholesterol sensor.	Because of its role in lipid metabolism, it is linked to atherosclerosis, myocardial infarction, and Alzheimer's disease
	5. CD23	1. Evokes allergic reaction via histamine release. 2. Immune response regulation by internalization of IgE complexes.	1. It is associated with autoimmune disorders like rheumatoid arthritis, systemic lupus erythematosus. 2. *M. avium* promotes CD23 expression to promote its survival
Cytokine repertoire and cytokine receptor	1. IL-1RA (receptor: IL-1R)	1. Endogeneous antagonist to IL-1. 2. Subdues inflammation and tissue damage.	Enhances the proliferation of prostate cancer cells
	2. IL-10 (receptors: IL-10RI and IL-10RII)	Suppresses immune response.	1. Impedes pathogen clearance. 2. Breast and cervical cancer progression
	3. Decoy IL-1R type-II receptor	Inhibition of IL-1 signaling.	Induces angiogenesis in colon cancer.
Chemokine repertoire and chemokine receptors	1. CCL24 (receptor: CCR3)	Chemotaxis of eosinophils, neutrophils, and lymphocytes.	Associated with carcinoma of head &neck and GIT.
	2. CCL17 & CCL22 (receptor: CCR4)	1. Recruitment of T-cells. 2. Inactivation of the CCR4 receptor	1. Linked to idiopathic pulmonary fibrosis. 2. Enhancement of metastatic potential of tumor cells.
	3. CCL16 (receptors: CCR1, CCR2, CCR5, and CCR8)	Chemoattractant for eosinophils	1. Induces pertussis 2. Enhances angiogenesis and metastasis in neuroblastoma. 3. Induces chemoresistance in breast cancer.
	4. CCL18 (receptor: CCR8)	T-cell recruitment	Promotes invasion and metastasis in breast cancer.

and Xie in the early '90s discovered inducible nitric oxide synthase (iNOS) in murine macrophages in response to cytokines and microbial products [21]. It converts arginine to L-citrulline, NO and reactive nitrogen species thereby rendering macrophages cytotoxicity to pathogens. Now it is well known that M1 and M2 macrophages perform diametrically opposite functions with these two biochemical molecules, i.e., NO and ornithine. M1 macrophages mediate fight response via iNOS (inducible nitric oxide synthase) by producing NO inhibiting cell proliferation whereas M2 macrophages mediate fixing response via arginase-I producing ornithine promoting proliferation and repair. This pathway is central to macrophage polarization that arginine is said to be “fork in the road” and the intermediates of each enzyme inhibits the opposing pathway [13]. In humans, arginase is found in peripheral blood mononuclear (PBMCs) fraction after injury [22] and is associated with immunosuppression related to maintaining homeostasis [23]. In hepatocytes, where urea cycle takes place, arginase-I is presented in cytosol whereas in macrophages it is inducible and is induced by Th2 cytokines IL-4, IL-10, IL-13, PGE2 and cAMP [24,25]. IL-4 and cAMP act synergistically to induce arginase-I as STAT 6 and C/EBPB binds to IL-4 response elements of the arginase-I gene. PI3K is universally associated with M2 polarization which is also linked to its role in TLR4 signaling [26]. Also, deletion of PTEN (Phosphatase and tensin homolog) leads to M2 polarization via C/EBPβ and STAT3 [27]. Ornithine provides the raw material for replication, protein translation, cell growth, and differentiation. Thus arginase expressing macrophages are involved in wound healing [28] and tumor growth [29]. Macrophages associated arginase-I promotes the growth of Leishmania inside murine macrophages via the synthesis of polyamines [30]. The arginase is a marker for visceral leishmaniasis and HSV (Herpes simplex virus) infection. Although tissues resident macrophages constitutively express arginase-1 [31]. In Cardiovascular pathologies including hypertension, atherosclerosis, and myocardial ischemia, it has been demonstrated that arginase inhibition increases NO bioavailability reducing oxidative stress and improves vascular functions as nitric oxide acts as a vasodilator [32]. Tumor-associated macrophages (TAMs) include a subset of Tie2-expressing macrophages (TEMs) which express Arg-1 and are known to be anti-inflammatory and angiogenic [33]. TAMs which are predominantly M2 polarized express high amount of Arginase-1 and the arginine is critical for T-cell function. As there is decreased arginine levels from macrophages associated with tumor, there is a decrease in arginine levels in CD8T-cells, thereby enhancing their anti-tumor activity. Hence TAMs which secrete Arginase-1 are hypothesized to reduced local anti-tumor activity [34].

2.1.2. COX-2

Cyclooxygenase (COX) is an enzyme that catalyzes the formation of prostaglandins from arachidonic acid leading to pain, spasm, and inflammation via activation of G-protein coupled receptors [35]. COX exists in two isoforms, i.e., COX-1, which is constitutively expressed and COX-2, which is inducible and is not detectable in normal tissues [36]. Role of COX-2 has been reported in various pathologies like cancer [36], atherosclerosis [37] and Alzheimer's disease [38]. Subsequent to injury, COX-2 is expressed in epithelial cells and becomes predominant isoform in these cells. These epithelial cells become migratory and move towards the site of injury [39]. Reportedly, COX-2 also has physiological functions which include rennin production [40], determines brain structure [41] and maintains gastric integrity. In human and murine macrophages COX-2 is induced following stimulation with LPS and phorbol esters. PKC-α is one of the important kinases regulating the expression of COX-2 in macrophages [42], but the detailed mechanism remains obscure. However, it has been suggested that may be inflammatory signals modulate the transcription regulation of COX-2 genes. A large quantity of PEG_2 is generated in macrophages due to upregulation of COX-2 following an inflammatory insult. Upregulation of COX-2 involves an essential role of NF-κB and EGR-1(Early growth response-1) leads to PGE_2 production by macrophages [43]. The cAMP is a major intracellular second messenger signaling in macrophages which results in decreased synthesis of pro-inflammatory cytokines [44].

Tumor-associated macrophages (TAMs) exhibit a predominantly M2 phenotype [45] which assist metastasis and angiogenesis. Macrophages are a major source of COX-2 in colorectal cancer [46]. Effect of COX-2 inhibition on TAMs altered cytokine profiles by reeducating M2 TAMs to M1 phenotype in the tumor microenvironment [47]. Further COX-2 in TAMs promotes survival of breast cancer cells by increasing Bcl-2 and p-gp along with decreasing Bax in these cells. In turn, COX-2 in breast cancer cells promotes M2 macrophage polarization of TAMs suggesting COX-2 as a key promoter triggering positive feedback between macrophages and cancer cells [48]. Later it was established that COX-2 inhibition caused loss of M2 macrophages characteristics of TAMs causing abatement in metastasis to lungs [49]. COX-2/PEG_2 causes activation of the PI3K/Akt pathway and COX-2+ TAMs induce PI3K/Akt activation in breast cancer cell increasing their survival [50].

2.1.3. Suppressor of cytokine signaling (SOCS)

Cytokines are class of glycoproteins regulating fundamental biological functions via binding to plasma membrane-bound receptor. The signaling from the plasma membrane is transmitted to the nucleus most commonly via the JAK-STAT pathway which is linked to various autoimmune disorders and cancer [51]. Cytokine inhibition is achieved by protein inhibitors of activated STATs (PIAS) which comprises of (i) Src-homology 2 (SH2)-containing protein tyrosine phosphates (SHPs) and suppressor of cytokine signaling (SOCS). The SOCS family comprises mainly of cytokine-inducible SH2 protein (CIS) and SOCS-1, SOCS-2 and SOCS-3. These are induced upon stimulation by cytokines and inhibit the production of the same cytokine via a negative feedback mechanism [52]. They have been paired according to the similarity in their amino acid sequences and structure into CIS and SOCS-2 and SOCS-1 and SOCS-3. SOCS-1 and SOC-3 are specific as they have no introns and possess a kinase inhibitory region. SOCS proteins negatively regulate Interferon-γ signaling and T-cell differentiation. It is a critical regulator of post-natal growth and fetal liver haematopioesis [53].

It has been proposed that altered SOCS expression in macrophages results in altered functions linked to various conditions of health and disease. A high SOCS1 to SOCS3 ratio is a marker of M2 Polarized macrophages [54]. SOCS1 controls PI3K activity which is required for arginase-1 expression in M2 macrophages. SOCS-1 deficient macrophages experience an upregulation in SOCS-3 expression resulting in PI3K inhibition and suppressing M2 polarization of macrophages [55]. IL-4 stimulus to macrophages upregulates SOCS-2 expression, which is supposedly involved in driving M2 macrophage polarization [56]. Macrophages deficient in SOCS-2 fight infection more efficiently because of NO production. There exist conflicting views on involvement of SOCS-3 in macrophages polarization as SOCS-3 deficiency in human and rodent macrophages could not produce pro-inflammatory mediators [57] whereas, SOC3 deficiency in mice promotes M1 macrophage activation [58]. Although activation of SOCS-3 blocks PI3K activation and augments M1 macrophage polarization suggesting that the argument is more in favor of its role in M1 macrophage polarization. Also in human tumors, SOCS1 positive macrophages promote tumor suppression whereas, SOCS-3 positive macrophages posses enhanced tumoricidal action of macrophages due to aberrant STAT3 activation [59]. SOCS3, induced by LPS and TNF-α, is also associated with inflammatory bowel disease [60]. Hence modulation of macrophage-specific SOCS1 and SOCS3 ration can provide a new opportunity for immunomodulatory therapeutics to target various pathologies.

2.2. Surface markers

Cell surface markers are proteins expressed on the surface of cells and are specific to a given cell type. Immunophenotyping technique is used to study specific proteins expressed on the cell surface in research and pathological laboratories. The term cluster of differentiation or CD was coined in a 1st international conference on human leucocyte differentiation and is used to define specific subsets of immune cells.

2.2.1. CD206 (mannose receptor)

CD206 also known as C-type lectin or mannose receptor (MR) is defined by its ability to recognize mannosylated and fucosylated glycoproteins and their engulfment [61]. It is a 175 KD protein, and its features include a typical hydrophobic signal peptide, a cysteine-rich NH2-terminal region, a fibronectin type-II-like domain, eight carbohydrate recognition like domains, a hydrophobic transmembrane region and a cytoplasmic tail [62]. Mannose receptor is mostly present on macrophages and dendritic cells [63,64]. Mannose receptor expression is modulated by the functional state of macrophages [65]. It is affected by the immunoglobulins like IgG2a and IgG2b which prompt mannose receptor synthesis [66]. Cytokines like stimulated T-cell products downregulate mannosyl-receptor mediated endocytosis [67] and pathogens [68].

CD206, i.e., mannose receptor lacks classical signaling motifs in its cytoplasmic tail; it mediates a variety of cellular responses by activating NF-κB, which represents host cell response to Pneumocystis. NF-κB translocates to nucleus which involves p50 and p65 NF-κB subunits which lead to I-κB phosphorylation and IL-8 release [69]. There also exists a cross-talk between C-type lectin receptor signaling and toll-like receptor signaling. Mannose receptor contributes to innate immunity by binding to carbohydrates on yeast, mycobacterium, and other gram − ve and gram + ve bacteria followed by their engulfment. In *Leishmania donovani* infection both virulent and avirulent promastigotes utilize MR for its internalization by macrophages and then its invasion [70]. It is well known that *Mycobacterium tuberculosis* survives in macrophages by inhibiting phagosome-lysosomes fusion. Mannose capped lipoarabinomannan inhibits phagosome maturation, and finally, MR blockade during phagocytosis leads to reversal of P-L fusion inhibition in human macrophages [71]. Mannose Receptor *knock down* mice do not show increased susceptibility to *Pneumocystis carinii* infection; hence this receptor is not necessary for phagocytosis [72]. Another major role of mannose receptor is clearing the blood of inflammatory cytokines, and in MR knockdown mice there are elevated levels of inflammatory cytokines in the blood, and thus it inhibits inflammation [73]. Decidual macrophages in Placenta expressing CD206 increase maternal tolerance of fetus [74]. In tumor microenvironment, macrophage polarization to M2 phenotype presenting TAMs occurs early in the development. However, MR does not drive macrophages to polarization but plays a role in early tumor development [75]. Hypoxic breast tumor derived cytokine oncostatin M enhances CD206 positive macrophages in tumor microenvironment via mTORC2 activation which assist breast tumor metastasis [76].

2.2.2. CD163 (haemoglobulin-hepatoglobin scavenger receptor)

CD163 which is also known by various names such as M130, P155, hemoglobin-hepatoglobin (Hb-Hp) scavenger receptor, macrophage-associated antigen, RM3/1 antigen, MM130, KiM8, Ber-MAC3, SM4 and GHI/61 [77]. It is classified under group B cysteine-rich scavenger receptor [78,79]. There are five different isoforms of CD163 differing in their cytoplasmic domain [77,80]. CD163 expressing macrophages are found to be present in brain, spleen, placenta, liver, and lungs [81]. It's expression decreases in response to TNF-α, INF-γ, LPS, TGF-β whereas IL-10, Glucocorticoids, and IL-6 enhances CD163 expression [82–87]. Chemokines like CCL-3 (MIP-1α) and CXCL-8, CXCL-4 regulate CD163 expression on monocytes/macrophages [83].

Signaling mechanism associated with CD163 has been identified as PI3K/Akt signaling leading to an increase in phosphorylation of Akt at serine 473 and IL-10 release [88]. The major role of CD163 is characterized as to maintain homeostasis [77]. Kristiansen et al. identified CD163 as a binding protein of Hp-Hb using liquid-affinity chromatography of solubilized membranes [89]. Hence this receptor efficiently removes free hemoglobin as it is toxic [90]. CD163 on macrophages also acts as an adhesion receptor for erythroblasts and hence play a regulatory role during erythropoiesis [91]. CD163 is associated with anti-inflammatory process [92] as it inhibits human T-lymphocyte activation and proliferation [93]. It also suppresses CD4+ T-helper cells [94]. Sequence profile analysis revealed that TWEAK (TNF like weak inducer of apoptosis) is similar to Hp-Hb complex which is a natural ligand of CD163 and flow cytometric analysis showed that human monocytes bind to TWEAK which confirmed that CD163 acts as a weak TWEAK receptor [95]. CD163 recognizes both gram-positive and gram-negative bacteria and triggers cytokine production hence having a function similar to Toll-like receptor (TLR) [96].

Droste et al. reported the presence of a soluble CD163 (sCD163) which is shed from the plasma membrane via activation of PKC leading to protease-mediated shedding of the receptor [97]. Serum concentration of sCD163 is a biomarker for systemic inflammatory response syndrome, sepsis, bacteriemia, mononucleosis, leishmaniasis and Crohn's disease [98]. Soluble CD163 increases in association with a non-calcified coronary plaque in men with chronic HIV infection [99]. Increased concentration of sCD163 has been found in patients with severe Gaucher's disease, an inherited lysosomal storage disorder leading to hepatomegaly and splenomegaly [100]. Multivariate analysis showed that there is positive co-relation in the expression of CD163 in breast cancer associated macrophages and poor prognosis [101]. Whereas rectal carcinoma associated macrophages expressing CD163, showed low apoptotic activity and led local recurrence and less survival [102].

2.2.3. CD204 (scavenger receptor A)

Scavenger receptors are primarily known to have a cleansing function by recognizing and modifying low-density lipoprotein by oxidation or acetylation. They were described by Joseph Goldstein to be present on macrophages and involved in uptake and degradation of LDL (low density lipoprotein) [103]. It is a trimeric transmembrane receptor made up of 6-domains [104] and charged collagen domain mediates recognition of acetylated LDL [105]. Scavenger receptor-A exits in two isoforms, i.e. scavenger receptor A type-I and scavenger receptor A type-II formed by differentiated splicing of same gene [106]. The signaling pathway activated by the binding of a ligand to scavenger receptor A requires tyrosine phosphorylation and increased protein kinase C activity. Scavenger receptor A (SR-A) mainly deals with the clearing of apoptotic bodies and sequestered inflammatory proteins as well as immature thymocytes. LPS, a surface molecule gram-negative bacteria, and LTA (lipoteichoic acid), a surface protein on gram-positive bacteria are recognized by SRA [107,108]. These receptors also aid adhesion of macrophages and have been found to increase the adherent property of 293EDNA cells [109]. In hepatic injury induced by concanavalin A, it has been found that scavenger receptor A attenuates T-cell differentiation and hence protects the liver [110]. Further, it has been demonstrated that fucoidan, binds to SR-A inhibits ER stress-induced autophagy by activating mTOR pathway [111]. SR-A contributes to atherogenesis as SR-A positive macrophages in arterial plaques secrete chemotactic factors and inflammatory cytokines [112]. SR-A amplifies inflammatory response in septic shock by getting physically associated with TLR4. This association activates gene88/NF-κB signaling [113].

2.2.4. Scavenger receptor B

Scavenger receptor B (SR-B) is expressed only in cells of lymphoid and hematopoietic lineages, but its expression is highest in macrophages. SR-B family includes three members SR-B1, SR-B2, SR-B3 (also known as CD36). Scavenger Receptor class B, type 1, is made up of 50 amino acids and is characterized by heavily N-glycosylated extracellular domain. SR-B1 is established as a major route for selective uptake of HDL (high density lipoprotein) cholesterol to the steroidogenic pathway [114]. As it is localized in caveolae of cells, which is a cholesterol sensor, SR-B1 hastily responses to modification in HDL by activating ERK1/2 protein kinases [115]. It has been shown that oxidized phospholipids accumulation induces oxidative stress which inhibits SR-B1 mediated cholesterol transport and worsens the atherosclerotic plaque scenario [116]. SR-B1 has been linked to coronary artery disease and atherosclerosis. Studies in SR-B1 knockdown mice showed that mice suffered from multiple myocardial infractions, heart enlargement and other electrocardiographic abnormalities [117]. Mice deficient of SR-B1 also showed enhanced lymphocyte proliferation, imbalanced interferon-γ (INF-γ) and interleukin-4 (IL-4) production in lymphocytes and hence they are implicated in autoimmune disorders [118]. SR-B1 also plays a role in recognition of hepatitis Virus [119]. CD36 is an 88KD, 472 amino acid transmembrane protein also known as FAT (Fatty acid translocase). CD36 acts as a receptor for thrombospondin-1 [120] and hence inhibits angiogenesis [121] and leads to apoptosis via MAPKs, i.e., p38 and c-Jun and caspase-3 [122,123]. CD36 is involved in recognition *C. elegans* and fungi [124]. It recognized lipoprotein components and termed as a sensor of diacylglycerides [125]. Because of its involvement in lipid metabolism, it is linked to atherosclerosis [126] and alzheimer's disease [127]. As it is most extensively studied in atherosclerosis, signaling mechanism involved in CD36 mediated foam cell formation involves Lyn and JNK. Van family of guanine nucleotide exchange factors (GEFs) are important intermediates which in turn are activated by Src-family kinases [128].

2.2.5. CD23

CD23 also named as FcεRII is a low-affinity receptor for IgE which exists as a dimer and it is involved in evoking allergic reactions via releasing histamine from mast cells, basophils and platelets [129]. It acts as a decoy receptor for IgE. It is a C-type lectin and IL-4 induces its expression on macrophage [130]. CD-23 is a 45-KD transmembrane receptor [131] and binds to the Cε3 domain in IgE [132]. Heteronuclear NMR spectroscopy revealed that CD23 consists of roughly orthogonal α-helices and eight β strands forming two anti-parallel β strands as well as two anti-parallel β-sheets [131]. Activation of CD-23 on macrophages targets IκBα hyper phosphorylation which activates transcription factor NF-κB [133,134]. CD23 has the ability to internalize IgE-antigen complexes thus has a role in the regulation of immune response. Elevated CD23 levels have been found to be associated with autoimmune disorders like rheumatoid arthritis, systemic lupus erythematosus or inflammatory components [135]. *Mycobacterium avium* promotes CD23 expression in macrophages through NO pathway activation hence inhibiting its killing [136].

2.3. Cytokine repertoire and cytokine receptor of M2 macrophages

Cytokines are a class of low molecular weight proteins secreted by cells affecting interactions and communication between cells. They are classified based on type of cells releasing them, i.e., lymphokines (lymphocytes), monokines (monocytes), chemokines (which have chemotactic activity) and interleukins (leukocytes acting on leukocytes) [137]. The polarization of macrophages is characterized by differential cytokine production [14,138]. Transcriptional profiling via high-density oligonucleotide microarray analysis revealed genes associated with alternative activation of macrophages [139]. Chemokines of M2 macrophages promote angiogenesis [140–142] tissue repair [143,144] and clearing of debris. Although M1 chemokine production is inhibited by M2 promoting signals [14,45], some ambiguity does exist in their release profile.

2.3.1. IL-1RA

As the name suggests IL-1RA is an antagonist to the IL-1 receptor, i.e. it will bind to IL-1R and thus inhibiting the binding of its agonist IL-1α and IL-1β, therefore, inhibiting their responses. X-ray diffraction study of the crystal structure of IL-1RA revealed that it contains two independent IL-1RA molecules [145]. There exist four structural variants of IL-1RA; a 17KDa (sIL-1RA) released from different leucocytes and three intracellular isoforms. Treatment of monocytes/macrophages with IL-4 in vitro leads to increased mRNA expression and release of IL-1RA [17]. IL-1RA given *i.v.* to rabbits inhibited the leucocyte recruitment in the synovial lining and joint cavity [146]. Other studies provide evidence of the role of IL-1RA as an important tool in subduing inflammation and tissue damage caused mainly by IL-1 [147] defending the host against septic shock, IBD, graft versus host disease and RA (Rheumatoid arthritis) [148]. IL-1RA suppresses cytokines induced IL-1β and TNF-α release. Hence, decreasing the responsiveness of macrophages to pro-inflammatory signals [149]. IL-1 retards the growth of prostate cancer cell. By blocking IL-1 interaction with its receptor, IL-1RA enhances proliferation of prostate cancer cells [150].

2.3.2. IL-10

IL-10, which is a well-known cytokine inhibiting the activity of Th1 cells, NK-cells and macrophages thereby providing protection against tissue damage, although this impedes pathogen clearance. Hence it is an immunoregulatory component of the immune system. It is produced by macrophages, dendritic cells, B-cells and Tregs. It regulates T-cell response by inhibiting MHC class II and co-stimulatory molecules B7-1, B7-2 expression on monocytes and macrophages limiting their pro-inflammatory cytokines profile [151,152]. IL-10 acts on CD4+ T cells by inhibiting their proliferation and production of IL-2, INF-γ, IL-4, IL-5 and TNF-α [152–154].

Macrophages express IL-10 following activation of specific pattern recognition receptors (PRRs), activated by pattern derived products from pathogen [155,156]. ERK signaling is one of the major cascades associated with IL-10 expressed via macrophages. ERK deficient cells have decreased IL-10 production [157]. This induction of IL-10 by ERK is supported by NFKB-1 which activates ERK [158,159]. Major transcriptional factors controlling IL-10 production by macrophages are MAF, CREB, SP1, C/EBP, ATF1, PBX1 [160]. IL-10 regulates its anti-inflammatory response by selectively inhibiting transcription of its targets TNF-α, IL-6, IL-12p40, and various chemokine mRNAs [161].

IL-10 from macrophages allows long term escape of pathogens from immune control leading to their persistent infection in case of *Candida albicans* and Mycobacterium infections [151]. It favors pathogen clearance and downstream pathologies in the case of *Toxoplasma gonadii*, malaria and Leishmaniasis [162,163]. In lung cancer patients high levels in serum or tumor is associated with worse survival [164]. High levels of IL-10 mRNA are detected in both breast and cervical cancer [165].

2.3.3. Decoy IL-1R type-II receptor

Decoy receptors possess binding affinity to the ligand but are incapable of activating a signaling cascade [166] and are also called death receptor to be identified [167]. Decoy IL-1RII receptor was the first decoy receptor to be identified [167] IL-4, IL-13 and glucocorticoid hormones increase expression of decoy receptor IL-1RII on macrophages [168]. This receptor binds to IL-1β with a lower affinity compared to IL-RI [132], but its binding is irreversible [169]. Hence the main function of IL-1RII is inhibition of IL-1 signaling which contributes to pathologies of inflammatory diseases like RA, gout, and psoriasis [170]. Its role has been described in various diseases associated with inflammation. It has a beneficial role in arthritis [171], endometriosis [172]. IL-1RII has been demonstrated to act with c-fos leading to enhanced expression of IL-6 and VEGF-A (vascular endothelial growth factor-A) in colon cancer inducing angiogenesis [173].

2.4. Chemokines and chemokine receptor

Chemokines are members of cytokine family which display chemotactic property that stimulates recruitment of leucocytes [174]. They are classified into CC family (i.e., MCP-1 family) and CXC chemokines family (i.e., interleukin-8 family) [175]. Chemokine receptors are known to be G-protein coupled receptors [176], and mainly signal transduction is through phospholipase C pathway [177]. M2-inducing signals exhibit release of distinct chemokine repertoire [14]. Anti-inflammatory cytokines IL-4 and IL-13 selectively induce the release of CCL17, CCL22, and CCl24 [178]. All the chemokines release by M2 macrophages basically help in tissue repair and remodeling, immunoregulation, allergy and tumor progression [14]. IL-10 suppresses transcription of M1 cytokines via STAT 6 which sequesters molecules which are required for STAT1 [179].

2.4.1. CCL24

Chemokine ligand 24 is also known as eotaxin-2 and myeloid progenitor inhibitory factor-2 (MPIF-2) or eosinophil chemotactic protein-2. It was initially cloned from a library of activated macrophages. It interacts with CCR3 on eosinophils inducing chemotaxis in these cells [180]. It can also induce chemotaxis in neutrophils and lymphocytes [181]. This is mediated via activation of P42/44 MAPK activity in eosinophils. It is an important diagnostic marker of asthma and aspirin-exacerbated respiratory diseases [182]. This CCL24 mediated activation of eosinophils is associated with malignancy of head & neck and gastrointestinal tract [183]. Rho B and VEGFA activation regulate CCL24 effect on hepatocellular carcinoma [184].

2.4.2. CCL22 and CCL17

Chemokine ligand 22 known as macrophage-derived chemokine (MDC) is a CC family member is upregulated by microbial products and Th-2 type cytokines IL-4 and IL-5, prostaglandins and cAMP-elevating agents [185].CCL17, also known as thymus activation-regulated chemokine (TARC) is also a CC-chemokine. Both CCL22 and CCL17 act as an agonist to CCR4 and are important for the recruitment of T cells. They both inactivate CCR4 by causing its internalization although they differ in their potency of inactivation and mechanism of internalization [186]. CCL17 and CCL22 have been linked to IPF (idiopathic pulmonary fibrosis) as the levels of CCL17, CCL22 and CCR4 were significantly higher in IPF patients and local expression of CCL22 induced lung dysfunction via recruitment of alveolar macrophages [187]. They play a major role in the recruitment of Foxp3+ Tregs (T cells) in gastric cancer which results in impairment of anti-tumor immunity [188]. It has been reported that breast cancer metastasizing to lung metastasis

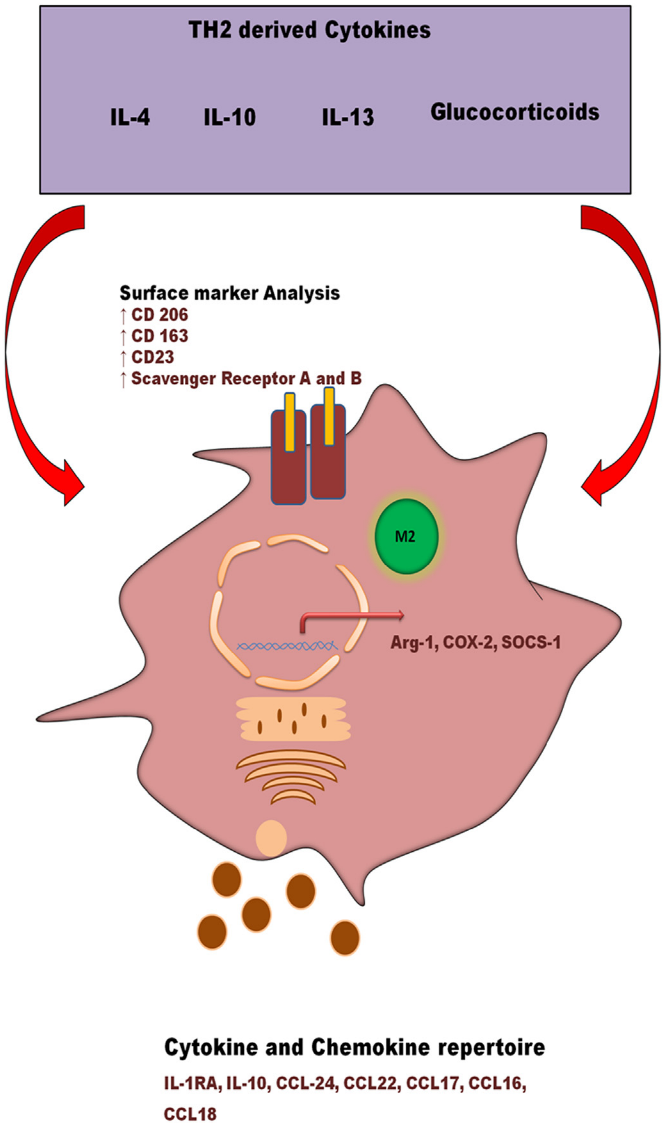

Fig. 2. Graphical abstract demonstrating markers of M2 macrophages.

requires expression of chemokine receptor CCR4. Here the tumor at the primary site, i.e. mammary fat pad activates expression of CCL17 and CCL22 in lung attracting both tumor and immune cells [189]. The activation of CCR4 by these macrophage secreted chemokines activates PI3K signaling which is necessary for T-cell recruitment [190].

2.4.3. CCL16

It is also known as liver-expressing chemokine (LEC) and monoactin-1 (MTN-1). IL-10 induces CCL16 in M2c human macrophages [191]. CCL16 is a chemoattractant for eosinophils activation via histamine receptor IV [192]. It interacts with other chemokine receptors such as CCR1, CCR2, CCR5, and CCR8 [193]. It has been demonstrated that CCL16 induced pertussis toxin-sensitive calcium mobilization and chemotaxis in murine L1.2 cells is mediated by histaminic H4 receptor [194]. CCL16 is considered to be an angiogenic chemokine [195]. CCL16 primes HUVECs to the mitogen activity of VEGF-A [196]. Neuroblastoma cell metastasizes to the lymph node is mediated via interaction between via interaction between CXCR5 and CCL16 [197]. CCL16 deficiency decreases and reduces chemo-resistance. In breast cancer, CCL16 knockdown mice have a smaller tumor and less lung metastasis [198].

2.4.4. CCL18

CCL18 is a CC chemokine also known as PARC (pulmonary and activation-regulated chemokine), derived cell chemokine-1 (DC-CK-1) and MIP-4 (macrophage inflammatory protein-4). CCL18 recruits T-cells via unidentified receptors [199]. Studies on esophageal biopsy tissues confirm the interaction of CCL18 and CCR8 establishing it as one of the targets of CCL18 via internalization of CCR8 leading to calcium flux [200]. PITPNM3 also known as Nir, was identified as a functional receptor for CCL18 in breast cancer and associated with promoting invasion and metastasis of breast cancer xenografts. It is also expressed in human retina, brain, spleen, and ovary [201]. It is found to be overexpressed in breast cancer cells explaining CCL18-PITPNM3 interaction as a crucial event in enhancing invasion and metastasis [202]. Treatment of prototype model of endothelial cells HUVECs (human umbilical vein endothelial cells), which are a model to study angiogenesis with CCL18 induces their endothelial to mesenchymal transformation via activation of ERK and Akt/GSK-3β signaling. As TAMs secrete CCL18, they promote angiogenesis and tumor progression [201].

3. Conclusion

To conclude the above discussion, it can be culminated that the above-discussed markers can be used as a definition to a distinct subset of macrophage known as alternatively activated macrophages or M2 macrophages. Fig. 2 sums up the above details. These marker discussed here provides the functionally diversified roles served by M2 polarization macrophages in both physiological and pathological events. Though therapeutic targeting of altered macrophages phenotype is still in infancy, detailed study of these molecules along with their detailed mechanism may be helpful in devising immunomodulatory approaches to various health dispositions.

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Declaration of interest

No potential conflicts of interest were disclosed.

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